Male sex hormones in ovaries essential for female fertility

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Male sex hormones, such as testosterone, have well defined roles in male reproduction and prostate cancer. What may surprise many is that they also play an important role in female fertility. A new study finds that the presence and activity of male sex hormones in the ovaries helps regulate female fertility, likely by controlling follicle growth and development and preventing deterioration of follicles that contain growing eggs.

This study and others highlight the fact that women need certain levels of male hormones, or androgens, in their bodies to function normally. The current study, published today in the journal *Molecular Endocrinology*, points to irregular androgen levels in the ovaries of female mice as a major cause of infertility. Understanding how male hormones influence ovulation in mice may provide clues as to how to better regulate androgens and combat infertility in humans.

"The need for certain levels of male hormones in the female body and the strong influence these hormones have is often underappreciated," said Stephen Hammes, M.D., Ph.D., Louis S. Wolk Distinguished Professorship in Medicine (Endocrinology and Metabolism) at the University of Rochester Medical Center and a lead author of the study. "Our findings open up a new line of research into how we can regulate male sex hormones, specifically in the ovaries, to improve fertility."

These findings are relevant to women who suffer from polycystic ovarian syndrome (PCOS), a condition characterized by androgen excess. PCOS is marked by the overproduction of male hormones and

causes ovarian changes that prohibit regular ovulation, often contributing to infertility. Hammes, chief of the Division of Endocrinology and Metabolism at the University of Rochester, believes that better understanding the overall effects of androgen levels in the ovary may help researchers determine how to target and control the increased levels that lead to fertility problems in women with PCOS.

Polycystic ovarian syndrome is the No. 1 cause of infertility in women. The condition affects 5 percent to 10 percent of women of childbearing age and is nearly as common as (and often associated with) Type 2 diabetes. Overall, more than 6.1 million women in the United States ages 15 to 44 have difficulty getting pregnant or staying pregnant, according to the Centers for Disease Control and Prevention.

The current research builds on past studies, some of which were performed in the laboratory of Chawnshang Chang, Ph.D., at the University of Rochester, which have shown that completely eliminating male hormone receptors, or androgen receptors, in female mice leads to abnormal ovarian function and reduced fertility. To help determine which reproductive tissues, including the hypothalamus, pituitary, and many cells within the ovary, regulate fertility, authors of the current study removed androgen receptors from only ovarian cells, known as granulosa cells, in female mice. Androgen receptors in all other reproductive tissues, including the hypothalamus, pituitary, and other ovarian cells were left intact.

Female mice without androgen receptors in the ovarian granulosa cells had premature ovarian failure, meaning they stopped ovulating too early, and were sub-fertile, meaning they had abnormal ovulation cycles, did not ovulate as many eggs as control mice, and had smaller litter sizes. These mice also had fewer follicles that completed development and were ready to ovulate; rather, many of their follicles did not progress beyond pre-development stages and died before ovulation could occur.

These results suggest that the presence of male hormones in ovarian granulosa cells in mice is critical for normal follicle development and fertility. When androgen receptor signaling is blocked or eliminated in ovarian granulosa cells, ovarian follicles cannot progress to later stages of development, ultimately resulting in reduced fertility.

"We found that fertility problems are most likely present because androgen signaling in the ovary is abnormal," said Aritro Sen, Ph.D., research assistant professor in the division of Endocrinology and Metabolism at the University of Rochester Medical Center and a lead author of the study. "Previously, we assumed that androgen signaling in the brain - the hypothalamus and the pituitary - was at the root of the problem, but we found that is not the case."

Provided by University of Rochester Medical Center